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Survival of Dental Implants in Bisphosphonate Users Versus Non-Users: A Systematic Review

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Abstract - *To investigate the literature regarding the survival rate of dental implants in bisphosphonate users as compared to non-users. An online search of literatures through MEDLINE-PUBMED (1950-March 2012), Cochrane Database of Systematic reviews, the Cochrane Central Register of Controlled Trials (CENTRAL) (1800- March 2012) and EMBASE (1966-March 2012) databases was performed. All the relevant publications were identified and full texts of these articles were obtained. After scrutinizing the relevant articles and their related references five articles that fulfilled the inclusion criteria were finalized. Only one study stated that dental implant failure was higher in patients under bisphosphonate therapy. The implant survival rates ranged between 95% and 100% in case of bisphosphonate users and 96.5% to 99.2% in non-users. Within the limitations of this review, it can be concluded that short term bisphosphonate therapy does not increase or decrease the survival rate of dental implants in bisphosphonate users as compared to non-users.*

KEYWORDS: Bisphosphonates, Dental implants, Osteonecrosis

INTRODUCTION

The bisphosphonates, in the past erroneously called diphosphonates, have been known to chemists since the middle of the 19th century, the first synthesis dating back to 1865 in Germany [1]. Bisphosphonates have been used in the chemical industry as anticorrosive and antiscaling agents as they inhibit the formation of calcium deposits on various surfaces. However, it was not until the 1960s that these agents were first considered for the treatment of human disease [2]. Fleisch *et al* [1], in 1968 first reported the biological effects of bisphosphonates. Bisphosphonates are potent osteoclast inhibitors and are considered the first choice therapy in diseases affecting bone metabolism such as osteoporosis and Paget's disease, as well as malignant tumors such as multiple myeloma, malignant hypercalcemia and others with bone metastasis such as prostate and breast cancer [3]. Alternate Indications for bisphosphonates therapy include giant cell lesions of the jaws, osteogenesis imperfecta, fibrous dysplasia, Gaucher's disease and osteomyelitis [4].

The two main categories of bisphosphonates are non-nitrogen-containing and nitrogen-containing bisphosphonates [5, 6]. Non-nitrogen-containing bisphosphonates function by competing with ATP in osteoclasts and triggering apoptosis in these cells, thus reducing bone resorption [7]. According to Reszka and Rodan[8], nitrogen-containing bisphosphonates inhibit farnesyl diphosphate synthase enzyme of the cholesterol biosynthesis pathway and disrupt the isoprenylation branch pathway which inhibits proteins and other factors that play a rate-limiting role in osteoclast resorption of bone. Also, nitrogen-containing bisphosphonates inhibit tumour proliferation and angiogenesis [9, 10].

Bisphosphonates may be administered by oral or intravenous (IV) routes. Oral bisphosphonates are used in the treatment of diseases such as osteoporosis and Paget's disease, whereas intravenous bisphosphonates are administered to patients with bone metastasis, multiple myeloma, breast cancer and malignant hypercalcemia [6]. Some of the commonly prescribed bisphosphonates are etidronate(oral), clodronate(oral/IV), tiludronate(oral), pamidronate(IV), alendronate(oral), ibandronate (oral/IV), risedronate(oral) and zoledronate(IV) [3].

A devastating complication of long-term bisphosphonate therapy is osteonecrosis of jaw. According to the American Association of Oral and Maxillofacial Surgeons [11], patients may be considered to have bisphosphonate related osteonecrosis of the jaw (BRONJ) if the patient is undergoing or had been previously treated with a bisphosphonate, has exposed bone in the maxillofacial region that persists for more than 8 weeks and has no history of radiation therapy to the jaws. Marx *et al* [12], in 2003 described the first cases of BRONJ. This was followed by reports of BRONJ by many authors [13-15]. IV bisphosphonates have been implicated in majority of the cases of osteonecrosis of the jaws [16].

The administration of Oral BP, such as alendronate, can produce bone exposure after 3 years [17]. Marx *et al*. [17], claim that for patients taking bisphosphonates, osteonecrosis seems to be related to a lack of vascular supply in combination with a lack of bone remodeling and regeneration. The study stated that complete prevention of this complication is not possible and the bone exposures after dental implants placement were 3.4%.

The rehabilitation of patients with dental implants for missing teeth has become a more attractive and efficient alternative to the conventional fixed and/or removable dental appliances [6]. Adults undergoing bisphosphonate therapy for various conditions is very common in today's scenario. Placement of dental implants in patients undergoing or who have undergone bisphosphonate therapy is still

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a controversy as the longevity of the implant over a period of time is questionable. This review aims at investigating the literature relating to the survival of dental implants in bisphosphonate users as compared to non-users.

MATERIALS AND METHODS

The objective of this article is to evaluate the literature relating to the survival of dental implants in bisphosphonate users when compared to non-users. Hence the question of interest is, is the survival rate of dental implants in bisphosphonate users increased or decreased as compared to non-users?

Literature search

The MEDLINE-PUBMED (1950-March 2012) database was searched for the pertinent literatures. This search was improved with a systematic search in the Cochrane Database of Systematic reviews, the Cochrane Central Register of Controlled Trials (CENTRAL) (1800- March 2012) and EMBASE (1966-March 2012) for English language articles. The keywords were used in various combinations like i) bisphosphonates, dental implants, survival rate, ii) dental implant, bisphosphonates, iii) bisphosphonates, oral implants, iv) bisphosphonates, dental implant failure, v) bisphosphonates, osteonecrosis. Titles and abstracts of the searches were screened by the two authors independently and checked for agreement. All the relevant publications were identified and full texts of these articles were obtained. Finally, a hand search of references cited in these articles was undertaken. As there is a very limited number of articles carrying information regarding the effect of bisphosphonates on the survival rates of dental implants, no validity analysis like meta analysis could be attempted. Hence this review presents the information in the form of description.

Inclusion and exclusion criteria

Longitudinal studies, systematic review articles and retrospective studies were included, whereas case reports, short case series, articles with improper study design, article for which no abstract was available, letters to editors and historic reviews were excluded.

RESULTS

The initial search resulted in 136 articles. After scrutinizing the relevant articles and their related references, five articles [18-22] that fulfilled the inclusion criteria were finalized. Data from these five articles [18- 22] were retrieved and has been summarized in table no.1. Four studies [18-21] were retrospective analysis and one study [22] had prospective research design.

In four studies [19-22] patients were on oral bisphosphonates for a mean duration of 3 years. No complications especially osteonecrosis were reported following dental implant placement. The most commonly used oral bisphosphonates by the patients were alendronate and risedronate. Out of the five studies [18-22], only one study [19] stated that dental implant failure was higher in patients under bisphosphonate therapy unless suggested safe guards were taken. The survival rate of dental implants in this study [19] was 86% in bisphosphonate users as compared to 95% in non users. Four studies [18-22] found no significant difference in survival rates of dental implants in bisphosphonate users and non-users. The implant survival rates ranged between 95% and 100% in case of bisphosphonate users and 96.5% to 99.2% in non-users. The follow up duration on an average was 3 years.

Table 1. *Summary of the selected studies on the survival rate of dental implants in bisphosphonate users and non-users*

Author, Year, Study design	*Number of Patients*		*Route/BP used*	*Survival rate*		*Conclusion*
	Users	*Non-Users*		*Users*	*Non-Users*	
Koka *et al.* 2010 (18) Retrospective	55	82	Not mentioned	99.17%	98.19%	Same survival potential in both the groups.
Kasai *et al.* 2009 (19) Retrospective	11	54	Oral, Alendronate	86%	95%	Dental implant failure higher in BP users unless suggested safeguards taken
Grant *et al.* 2008 (20) Retrospective	89	343	Oral, Alendronate, Risedronate, Ibandronate.	99.5%	99%	Comparable success rate for users and non-users
Bell & Bell 2008 (21) Retrospective	42	Not mentioned	Oral, Alendronate, Risedronate, Ibandronate.	95%	96.5%	Patients who take oral BP no more at risk of implant failure than other patients
Jeffcoat 2006 (22) Prospective	25	25	Oral, Alendronate, Risedronate,	100%	99.22%	No significant difference between the two groups

BP-Bisphosphonates, % - percent.

DISCUSSION

Bisphosphonates are an important group of drugs commonly used for treatment of metabolic and oncologic pathologies involving the skeletal system. They demonstrate the potential to over suppress bone turnover rates, inhibit angiogenesis and produce hypermineralized bone, thus impairing the reparative properties of bone [23-29]. Endosseous dental implants are replacing the conventional prosthetic appliances. However, the quantity and quality of the host bone and its healing capacity can influence the success rate and healing capacity of dental implants [30, 31]. The duration of bisphosphonate therapy appears to be an important factor in the manifestation of its complication – osteonecrosis, which may affect the survival rate of implants. The average duration of bisphosphonate therapy in the selected articles [18-22] is short term except in one study [18]. The American Society of Bone and Mineral Research [32], has defined long term oral bisphosphonate therapy as longer than 3 years.

Oral nitrogen containing bisphosphonates, alendronate and risedronate (and possibly more recently introduced ibandronate) demonstrate a risk for osteonecrosis [33]. Marx *et al* [33] have stated that exposure to alendronate for a mean duration of 5.7 years resulted in the osteonecrosis of the jaw and patients taking oral bisphosphonates for less than 3 years have little risk for osteonecrosis. Kasai *et al* [19] reported 86% success rate in bisphosphonate users as compared to 95% success rate in non-users. However, none of the cases developed osteonecrosis, the implants just failed to osseointegrate, but the study reviewed only 11 patients with dental implants who had undergone bisphosphonate therapy. However, contrary to this study, Koka *et al*. [18] state that the survival potential in bisphosphonate users and non-users is similar though the patients included were under bisphosphonate therapy for less than 3 years, 3-5 years and more than 5 years. On the other hand, the study could not assess the degree to which patients were compliant (adherence to medication regimens) and hence the true level of bisphosphonate exposure (in terms of duration) was unknown.

In the study by Grant *et al*. [20] no cases of osteonecrosis were reported and there were only two implants that failed to osseointegrate completely; of these, one patient had taken oral bisphosphonates for four years prior to surgery. Oral bisphosphonate therapy did not appear to significantly affect implant success. Bell & Bell [21] recorded 95% success rate of implants in bisphosphonate users compared to 96.5% in non users by the same operator. Out of the total 42 patients, five implants failed in five different patients. The duration of bisphosphonate therapy in three of these five patients was more than three years. However, other implants received by four of these patients at the same time osseointegrated successfully. The reasons for implant failure did not seem to be related to bisphosphonate therapy. This retrospective study showed no relationship between intake of bisphosphonates and implant failure.

In a longitudinal study, Jeffcoat [22] reported that the survival rate of implants after 3 years in bisphosphonate users was 100 % and not a single implant failed as compared to non-users. The survival rate of implants in non-users was 99.2%. This study too showed no correlation between bisphosphonate therapy and implant failure. The follow up duration in these studies is limited to about 3years. Bisphosphonates have relatively long half life. The effects of bisphosphonate therapy on dental implants cannot be determined by short term follow up period. Nevertheless, the risk of osteonecrosis in patients who have been administered bisphosphonates for longer than three years can be evaluated with the serum C- terminal telopeptide test (CTX) test [33]. Values greater than 150pg/ml allows for surgery to be performed under minimum risk without discontinuing the medication whereas values less than 150pg/ml suggest the deferment of surgery and discontinuation of the drugs for 4-6 months [33]. But a significant relation between this test and ostenecrosis in cancer patients treated intravenously with bisphosphonates was not found by Bágan *et al* [34].

According to the guidelines put forth by the American Association of Oral and Maxillofacial Surgeons [16], patients with less than 3 years of bisphosphonates intake are not contra indicated for implant placement. Whereas, patients on oral bisphosphonates for more than 3 years or less than 3 years and on corticosteroids, a "drug holiday" is recommended.

CONCLUSION

The potential risk of post treatment implant complications in patients under bisphosphonate therapy cannot be neglected. Within the limitations of this review, it can be concluded that short term bisphosphonate therapy does not increase or decrease the survival rate of dental implants in bisphosphonate users as compared to non-users. However, more longitudinal studies on long term bisphosphonate therapy in patients undergoing dental implant treatment will be needed to validate the implants survival compared to non-users.

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